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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/016,737	01/30/1998	GERALD P. MURPHY	8511-007	7366

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EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 08/24/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/016,737	MURPHY ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-37* is/are pending in the application.

4a) Of the above claim(s) *25 and 27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23,24,26 and 28-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *03/03/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

S.O.D

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 07/18/05 has been entered.

Accordingly, claims 23-24, 26, 28-37 are being examined.

The following are the remaining rejections.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, NEW MATTER

Claims 23-24, 26, 28-37 are rejected under 35 USC 112, first paragraph, as the specification does not contain a written description of the claimed invention.

The limitation of "no additional cytokine" claimed in Claims 23-24, 26, 28-37 has no clear support in the specification and the claims as originally filed.

A review of the specification discloses support for "the dendritic cells are cultured in the presence of GM-CSF and IL-4" (p.5, last paragraph, p.10, first paragraph, p.17, lines 25-26, p.22, third paragraph, p.27, paragraph before last). There is however no mention of "no additional cytokine".

It is noted that the courts have found that any negative limitation or exclusionary proviso must have basis in the original disclosure. The mere absence of a positive recitation is not basis for an exclusion. See *Ex parte Grasselli*, 231 USPQ 393 (Bd. App. 1983), *aff'd mem.*, 738 F.2d 453 (Fed. Cir. 1984).

The subject matter claimed in claims broadens the scope of the invention as originally disclosed in the specification.

REJECTION UNDER 35 USC 103

Rejection under 35 USC 103(a) of claims 23-24, 31-36 pertaining to being obvious over Cohen et al (US 5,643,786,of record), in view of Sallusto et al, 1994, J Exp Med, 179: 1109-1118, of record, and Inaba et al, Journal of experimental medicine (UNITED STATES) Jul 1 1987, 166 (1) p182-94, of record, remains for reasons already of record in paper of 06/17/04.

A. Applicant argues that the passage at column 10, lines 50-61 in Cohen et al is merely a broad summary statement of the prior work of others, and comparison of the prior results with calcium ionophore treatment.

Applicant recites column 10, lines 60-61, and table 3, step 8 in column 13, in Cohen et al. Applicant argues that in step 8, Cohen et al teach that specific recombinant cytokines combinations added to culture in some instances, for example rhIL-12, rhGM-CSF, rhIL-4 and rhIL-2. Applicant concludes that therefore, Cohen et al do not disclose or suggest a specific monocyte composition that is not related to monocytes exposed to calcium ionophore.

Applicant's arguments set forth in paper of 07/18/05 have been considered but are not deemed to be persuasive for the following reasons:

Cohen et al teach that certain specific combinations of cytokines have been successfully used to amplify (or partially substitute) for the activation/conversion achieved with calcium ionophore: these cytokines include rhIL-12, rhGM-CSF, rhIL-4 and rhIL-2., and that each cytokine when given alone is inadequate for optimal upregulation (column 10, lines 54-60).

In other words, this passage from Cohen et al clearly teaches that certain specific combinations of cytokines have been successfully used to amplify (or partially substitute) for the activation/conversion of monocytes, which could be also achieved with calcium ionophore.

In addition, in this passage, Cohen et al do not teach that the monocytes have to be treated first with calcium ionophore before treating with cytokines.

Further, step 8 teaches that **in some instances** (emphasis added) that the combination of cytokines rhIL-12, rhGM-CSF, rhIL-4 and rhIL-2 is added to monocytes that have been exposed to calcium ionophore. In other words, the teaching in step 8 in table 3 is applied only in some instances.

Although Cohen et al do not teach the details of how to activate monocytes exposed to prostate cancer cell lysate, this is compensated by Sallusto et al, who teach that the specific combination of GM-CSF and IL-4 provide the best conditions for the generation of cells with characteristic phenotypes and functional properties of dendritic

cells (p.1110, second column, last paragraph and table 1, on page 1112, which compares various cytokine combinations).

Thus, it would have been obvious to:

1) isolate the monocytes as taught by either Cohen et al, or Sallusto et al,

2) activate these monocytes using the specific combination of GM-CSF and IL-4 which provides the best results, as taught in the detailed method of Sallusto et al, as an alternative method to the calcium ionophore method of activating monocytes specific for prostate cancer antigen, taught by Cohen et al, in view of the teaching of Cohen et al that certain specific combinations of cytokines have been successfully used to amplify (or partially substitute) for the activation/conversion of monocytes, and further in view of successful activation of monocytes by GM-CSF and IL-4, taught by Sallusto et al, and

3) expose these monocytes to prostate cell lysate, as taught by Cohen et al, for them to present prostate tumor antigen, for potential use in prostate cancer treatment, as suggested by Cohen et al.

One would have a reasonable expectation of success in obtaining an activated dendritic cell population that could present prostate tumor antigen, in view of the teaching of Sallusto et al that exposure of monocytes or blood mononuclear cells to a combination of cytokines, such as GM-CSF and IL-4 would convert them to immature dendritic cells, that could efficiently present soluble antigen to activate specific T cells (Sallusto et al, abstract and p.1111, first column, first paragraph).

B. Applicant argues that Sallusto et al do not address tumor cell lysates or other tumor antigens and do not anticipate their use for therapeutic purpose.

This is not found to be persuasive. Applicant argues individual reference, rather than a combination of references.

Further, although Sallusto et al do not teach prostate cancer cell lysate antigen, this is compensated by Cohen et al, who teach that the activated monocytes could then be exposed to prostate tumor antigen for its presentation, for increasing the immune response to the tumor cells (Cohen et al, Example 2 on column 12).

C. Applicant argues that Cohen et al teach away from the invention, because Cohen et al compare various cytokine combinations as being inferior to calcium ionophores, and provide a prophetic example of a treatment method that cannot process and present any soluble antigen, much less a prostate tumor cell lysate.

The arguments are found not to be persuasive.

Contrary to Applicant arguments, Cohen et al do not teach away from the invention. Although, Cohen et al teach that no added other reagents, such as cytokines are as effective as calcium ionophore in upregulate the dendritic cell subpopulation, Cohen et al also teach that however, certain specific combinations of cytokines have been successfully used to amplify (or partially substitute) for the activation/conversion achieved with calcium ionophore (column 10, lines 54-60).

In other words, although cytokines, when added with calcium ionophore are not as effective as calcium ionophore, a certain combination of cytokines, when by themselves, without calcium ionophore, are successful to amplify or partially substitute for the activation dendritic cells, that could have been achieved with calcium ionophore.

Thus Cohen et al provide the motivation for substituting calcium ionophore with cytokines, with the teaching that a certain combination of cytokines are successful to amplify or partially substitute for the activation dendritic cells, that could have been achieved with calcium ionophore.

Concerning Applicant comment that Cohen et al provide a prophetic example of a treatment method that cannot process and present any soluble antigen, much less a prostate tumor cell lysate, it is noted that Applicant argues limitation not in the claims.

D. Applicant argues that Inaba et al do not provide any motivation for one to expect that the dendritic cells taught by Cohen et al or Sallusto et al would activate CD4+ or CD8+ T cells.

Applicant argues that T cell activation in Inaba et al only are ex vivo isolated dendritic cells, not dendritic cells that have been derived from in vitro cultured monocytes.

The arguments are not found to be persuasive.

Inaba et al clearly teach that dendritic cells are a major if not essential accessory cell for the activation of both subpopulations, CD4+ and CD8+ (figures 1-2 on page 184, and Summary on page 192).

Further, one would have expected that the dendritic cells activated in vitro by the method of Sallusto et al have the same properties and characteristics as isolated dendritic cells, taught by Inaba et al, because Sallusto et al teach that the specific combination of GM-CSF and IL-4 provide the best conditions for the generation of cells with characteristic phenotypes and functional properties of dendritic cells and are the

most efficient in presenting soluble antigen (p.1110, second column, last paragraph and table 1, on page 1112, which compares various cytokine combinations).

Applicant argues that Inaba et al describe the stimulation of T cells in a mixed lymphocyte reaction, a non-specific T cell activation, not an antigen-specific T cell activation. Applicant argues that Inaba et al do not describe the uptake or processing of any antigen, much less a prostate tumor cell lysate or an antigen-specific T cell activation as required by the present claims.

This is not found to be persuasive.

Inaba teach that they have studied "early events" in the activation of CD4+ and CD8+ T cells by dendritic cells (i.e. T cell proliferation and IL-2 production), and that antigen-specific CD8+ T cells can be directly induced to proliferate and become killer cells in the absence of a second population of helper CD4+ cells (Summary on page 192). Inaba et al further teach that dendritic cells induce the development of antigen-specfic CD4+ helper T cells, in addition CD8+ T cells, wherein the release of IL-2 by CD4+ helper cells is essential for the development of CD8+ T cells (p.182, first and second paragraphs).

Thus it is clear from the teaching of Inaba et al, that it is the properties of activated CD4+ and CD8+ T cells to be antigen-specific, and to function as killer cells.

In summary, since it is the properties of dendritic cells to activate CD4+ and/or CD8+ T cells, wherein said T cells are antigen-specific, and wherein said antigen could be any antigen, including a tumor antigen, one would have expected that the dendritic

cells taught by Cohen et al and Sallusto et al would activate prostate cancer antigen-specific CD4+ and/or CD8+ T cells.

Applicant argues that Inaba et al state that "of some interest is the role of dendritic cells in the primary response to viral or tumor antigens on other cells. Are antigens on infected or malignant cells presented directly to unprimed CD8+ T lymphocytes or via a dendritic cell in the host?".

The Examiner takes note that Applicant recites issue of in vivo activation by dendritic cells, a limitation not in the claims.

2. Claim 26 remains rejected under 35 USC 103 as being obvious over Cohen et al, in view of Sallusto et al, and Inaba et al, and further in view of Lutz et al for reasons already of record in paper of 08/20/03.

Applicant asserts that Cohen et al and Sallusto et al do not teach or suggest the dendritic cells of the present invention, and that Lutz et al adds nothing to render obvious the immortalized dendritic cells of the present invention.

Applicant's arguments in paper of 07/18/05 have been considered but are found not to be persuasive for the following reasons:

The claimed dendritic composition is obvious in view of the composition of dendritic cells taught by Cohen et al, Sallusto et al, and Inaba et al, *supra.*

Further, Lutz et al render the claimed immortalized dendritic cells obvious, because Lutz et al teach how to make immortalized dendritic cells to overcome the problem of being unable to maintain dendritic cells in vitro for long periods of time.

3. Claim 28-29 remain rejected under 35 USC 103 as being obvious over Cohen et al, in view of Sallusto et al, and Inaba et al, and further in view of Taylor et al for reasons already of record in paper of 08/20/03.

Applicant asserts that Cohen et al and Sallusto et al do not teach or suggest the dendritic cells of the present invention, and that Taylor et al adds nothing to render obvious the preserved dendritic cells of the present invention.

Applicant's arguments in paper of 07/18/05 have been considered but are found not to be persuasive for the following reasons:

The claimed dendritic composition is obvious in view of the composition of dendritic cells taught by Cohen et al, Sallusto et al, and Inaba et al, *supra.*

Further, Taylor et al render the claimed cryopreserved dendritic cells obvious, because Taylor et al teach how to cryopreserve dendritic cells for use in immunological procedures.

4. Claim 30 remain rejected under 35 USC 103 as being obvious over Cohen et al, in view of Sallusto et al, and Inaba et al, and further in view of Taylor et al and Lutz et al, for reasons already of record in paper of 08/20/03.

Applicant asserts that Cohen et al and Sallusto et al do not teach or suggest the dendritic cells of the present invention, and that there is no motivation to combine the cited references.

Applicant's arguments in paper of 07/18/05 have been considered but are found not to be persuasive for the following reasons:

The claimed composition is obvious in view of the composition of dendritic cells taught by Cohen et al, Sallusto et al, and Inaba et al, *supra*.

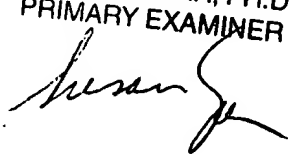
The motivation to combine the teaching of Cohen et al, Sallusto et al, and Inaba et al with Taylor et al and Lutz et al is for preserving the dendritic cells taught by Cohen et al and Sallusto et all, for use in immunological procedure, as taught by Taylor et al, and for immortalizing dendritic cells to overcome the problem of being unable to maintain dendritic cells in vitro for long periods of time, as taught by Lutz et al.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, JEFFREY SIEW can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SUSAN UNGAR, PH.D
PRIMARY EXAMINER



MINH TAM DAVIS

August 16, 2005